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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,520	BULUWELA ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,57,71-75 and 78-88* is/are pending in the application.

4a) Of the above claim(s) ____ is/are withdrawn from consideration.

5)☐ Claim(s) ____ is/are allowed.

6)☒ Claim(s) *53,57,71-75 and 78-88* is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on ____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-13-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: ____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: ____.

DETAILED ACTION

This Office action is in response to the communication filed 2-13-06.

Claims 53, 57, 71-75, 78-88 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 53, 57, 71-75, 78-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 8-9-05.

The claims are drawn to methods of suppressing expression of a selected gene in a eukaryotic cell comprising introducing into the cell a polypeptide comprising a nucleic acid binding portion which binds to a site at or associated with a selected gene and a chromatin inactivation portion, which chromatin inactivation portion is optionally limited to all or a N-CoR- or SMRT-binding part of PLZF, and which nucleic acid binding portion is optionally limited to a DNA binding part of a nuclear receptor DNA binding protein.

Applicant's arguments filed 2-13-06 have been fully considered but they are not persuasive. Applicant argues that adequate description has been provided for the instantly claimed invention on pages 44-50 of the instant specification. Contrary to Applicant's assertions, adequate description has not

been provided for the broad genus encompassed by the instantly claimed invention. The specification teaches a gene fusion construct comprising the PLZF coding region fused to the human estrogen receptor, ERα, and the gene fusion construct comprising the PLZF coding region fused to human androgen receptor (hAR). These fusion constructs are not representative of the broad genus comprising a polypeptide comprising a nucleic acid binding portion which binds to a site at or associated with a selected gene and a chromatin inactivation portion, and which genus provides for the function claimed, which function includes suppressing the expression of any selected gene in a eukaryotic cell and which chromatin inactivation portion facilitates histone deacetylation.

The portions of PLZF that bind to or facilitate recruitment of a HDAC complex have not been adequately defined or delineated in the art or in the instant disclosure. And the fusion constructs described and limited to the well-characterized ERα and AR nuclear receptor DNA binding proteins are not representative of the broadly claimed genus of DNA binding proteins from bacteria, yeast, animals and plants. No concise components from this broad range of purported class of nuclear receptor DNA binding proteins have been described so that a portion of the PLZF coding region fused to a DNA binding protein motif, and common to bacteria, yeast, animals and plants, have been described in the instant disclosure, and whereby their administration to a eukaryotic cell provides for suppression of expression of any selected eukaryotic gene. For these reasons, the written description rejection is hereby maintained.

Claims 53, 57, 71-75, 78-88 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the Office action mailed 8-9-05.

Applicant's arguments filed 2-13-06 have been fully considered but they are not persuasive. Applicant argues that the scope of the claims is fully enabled because a reduction of expression of endogenous estrogen-responsive genes in cell lines expressing PLZF-ER has been demonstrated in vitro. Applicant also argues that full enablement has been achieved because adequate predictability existed in the targeting and delivery of polypeptides to cells at the time of filing the instant application. Applicant asserts, for instance that transfection was a well known and routine method for intracellular delivery of polypeptides and proteins to eukaryotic cells. In support of this position, various publications have been provided, including Lundgren et al, TIPS, Vol. 21, pages 99-102, 2000 and J. Hawiger, Curr. Opin. Chem. Biol., Vol. 3, pages 89-94, 1999. Contrary to Applicant's assertions, neither the art, the instant disclosure nor the references provided in the IDS filed 2-13-06, including Lundgren et al and Hawiger, enable the full scope of the claimed invention.

The instant specification teaches a method of suppressing the expression of an estrogen responsive reporter gene in breast cells in vitro comprising the administration of a nucleic acid construct encoding PLZF- ERα (as described on p. 45 of the instant specification), and is enabled for a method of suppressing activation of an androgen responsive reporter gene in COS-1 cells in vitro comprising the administration of a nucleic acid encoding PLZF-AR, (as described

on p. 49 of the instant specification). These examples do not reasonably provide enablement for a method of suppressing the expression of any selected gene in any eukaryotic cell in vitro or in vivo comprising the administration of a polypeptide comprising any nucleic acid binding portion which binds to a site at or associated with a selected gene and any chromatin inactivation portion, which chromatin inactivation portion is optionally limited to all or a N-CoR- or SMRT-binding part of PLZF, and which nucleic acid binding portion is optionally limited to a DNA binding part of a nuclear receptor DNA binding protein.

The delivery of polypeptides to target cells in vitro, including the experiments described by Lundgren et al and Hawiger, are not correlative or representative of the ability to deliver the broadly claimed genus of polypeptides to appropriate target cells and in sufficient quantities in vivo, whereby selected gene expression is achieved in an organism. In vitro results cannot be extrapolated to in vivo success. The concentrations of polypeptides that can be introduced or provided to target cells in culture are not necessarily achieved in vivo. Contrary to Applicant's assertions, it requires undue experimentation beyond that provided in the art or in the instant disclosure to achieve in vivo suppression of any selected target gene in an organism by administration of a representative number of species of the broad genus of polypeptides claimed.

In addition to the unpredictability that remains to adequately deliver sufficient concentrations of the broadly claimed genus of polypeptides to target cells in an organism, Hawiger also teaches another level of unpredictability: the lack of importation of polypeptides to the nucleus in cells in vitro or in vivo using

cell permeable peptides (see esp. page 92, right hand col.). It is therefore unclear how the cell permeable peptides used successfully in vitro to enhance polypeptide delivery to the cytoplasm of cultured cells would be employed to successfully deliver adequate quantities of these polypeptides claimed to the nucleus of eukaryotic cells in vitro or in vivo, whereby successful suppression of selected genes is obtained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax

telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
4-24-06

JANE ZARA, PH.D.
PRIMARY EXAMINER

10/019,520

Annex 1: Further supporting data

Section 1: Establishment of MCF-7 cell lines expressing PLZF-ER in a tetracycline-inducible manner

PLZF-ER (as discussed in Example 1 of the application) was cloned into the TET-off plasmid pREVTRE (Clontech), which also confers resistance to hygromycin, and the recombinant plasmid stably transfected into the MCF7 TET-off (TO) cell line (Clontech). MCF7 is a human breast cancer cell line. Growth of MCF7 is dependent upon the presence of oestrogen in the growth media.

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In the presence of doxytetracycline (TET65; 100 μg/ml) in the growth medium, the transformed MCF7 cell lines constitutively expresses the TET repressor and represses expression of genes held in the pREVTRE plasmid. Three different populations of cells were selected for further investigation. MCF7 Pool is a pool of cells that survived hygromycin selection, whilst JP13 and JP23 are two representative and independent clones from that pool.

MCF-7-TO (the parental cell line), MCF7 Pool, JP13 and JP23 cells were transiently transfected with an estrogen-regulated reporter gene, chloramphenicol acetyl transferase (CAT), containing an ERE (ERE-G-CAT). Following removal of TET and/or the addition of 17ß-estradiol (E2; 10 nM) reporter gene activity was assessed and the data is presented in Figure 1 panel A. Reporter gene activity was similar in MCF7-TO in the absence or presence of TET and in the MCF7 pool, JP13 and JP23 cell lines in the presence of TET. In the absence of TET, however, reporter gene activity was significantly reduced in the MCF7 pool, JP13 and JP23 cell lines. The results represent at least 3 independent experiments. In each experiment ER activity in the presence of E2 was taken as 100%. All other activities are shown relative to this.

To confirm that the changes in CAT activity were associated with PLZF-ER protein levels, immunoblotting of whole cell extracts prepared from MCF-7-TO, MCF7 pool, JP13 and JP23 cells grown in the presence or absence of TET was performed using an anti-PLZF antibody. The results are presented in Figure 1, panel B.

The data shows that TET+ oestrogen (E2)+ cells have CAT reporter gene activity. This is due to the TET repressing the expression of PLZF-ER from the pREVTRE plasmid and E2 inducing transcription of the oestrogen-responsive CAT reporter gene.

When TET is omitted from the growth media then PLZF-ER is transcribed and, in the case of E2+ cells, the PLZF-ER protein is activated and blocks transcription of the CAT reporter gene. In the absence of E2 no CAT activity is recorded as oestrogen is required to activate the reporter gene and to activate PLZF-ER.